



PhagoBurn

EVALUATION OF PHAGE THERAPY FOR THE TREATMENT OF *Escherichia coli* OR *Pseudomonas aeruginosa* WOUND INFECTIONS IN BURNED PATIENT

Dr Patrick JAULT
Anesthesiology - Critical care

HIA PERCY CLAMART FRANCE

National Institute of Allergy and Infectious Diseases
BACTERIOPHAGE THERAPY
JULY 20-21 2015



*Votre vie,
notre combat*



MINISTÈRE
DE LA DÉFENSE

The opinions or assertions contained
herein are the private views of the
author and are not to be construed as
official or as reflecting the views of the
French ministry of defense

National Institute of Allergy and Infectious Diseases
BACTERIOPHAGE THERAPY
JULY 20-21 2015



*Votre vie,
notre combat*



DISCLOSURE

» The research leading to these results has received funding from the European Community's Seventh Framework Programme FP7 (2007-2013) under grant agreement n°601857 (3.8 M€)





*Votre vie,
notre combat*



PLAN

1. Rationale: threat and targets
2. Clinical study
3. Situation



*Votre vie,
notre combat*



I- RATIONALE: THREAT AND TARGETS



MINISTÈRE
DE LA DÉFENSE

National Institute of Allergy and Infectious Diseases
BACTERIOPHAGE THERAPY
JULY 20-21 2015



Votre vie,
notre combat



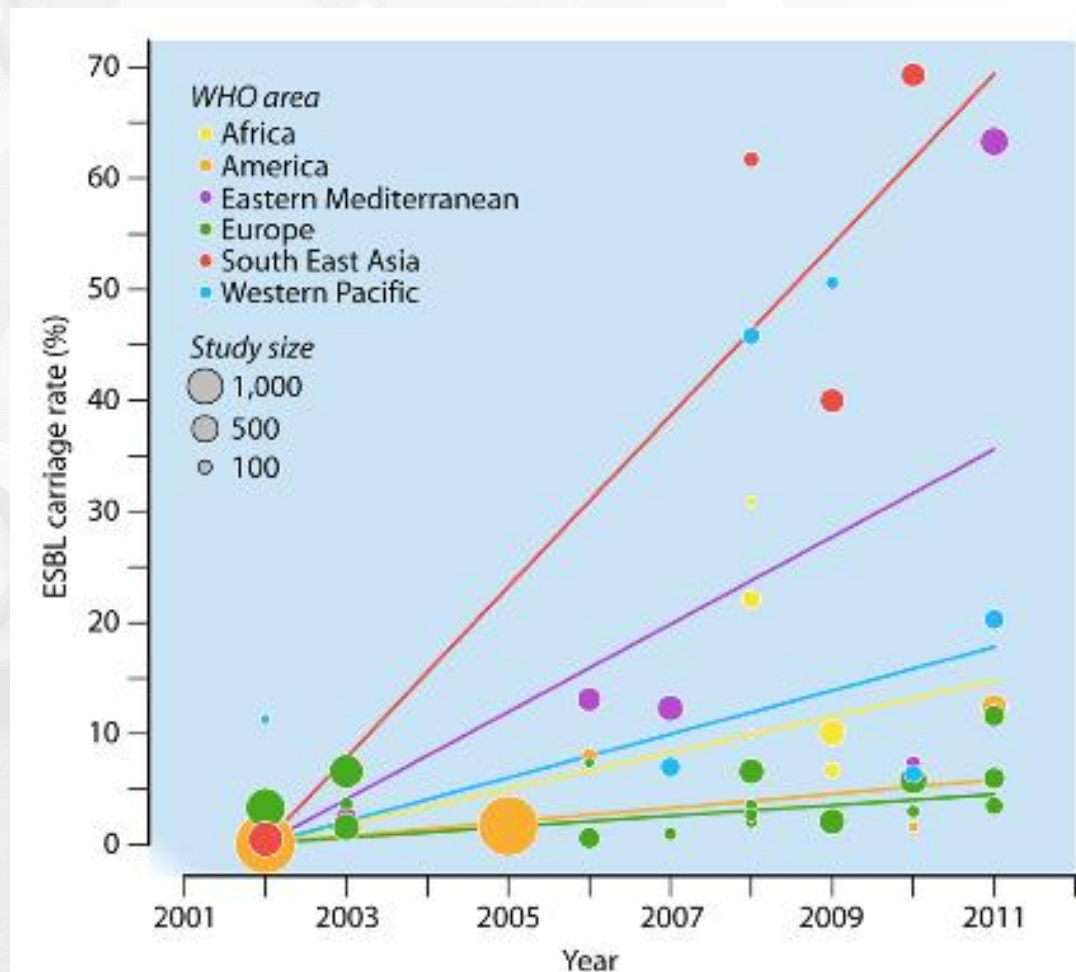
LESSONS FROM WAR

- » **Emergence of multidrug resistance in bacteria and impact on antibiotic expenditure at a major army medical center caring for soldiers wounded in Iraq and Afghanistan.** Zapor and al. Infect Control Hosp Epidemiol. 2008 Jul;29(7):661-3.
- » **Multidrug resistant bacteria in wounds of combatants of the Libyan uprising.** Frankea EA and al. J Infect. 2012 Sep;65(3):279-81.
- » **Colonization of Libyan civil war casualties with multidrug-resistant bacteria.** Koole K and al. Clin Microbiol Infect. 2013 Jul;19(7):E285-7.

*Continous emergence of threat froms battle zones to
hospital*



CIVILIAN DATA



Trends in human fecal carriage of extended-spectrum β -lactamases in the community: toward the globalization of CTX-M. Woerther PL and al. *Clin Microbiol Rev.* 2013 Oct;26(4):744-58

CIVILIAN ANSWER IS WAAAR

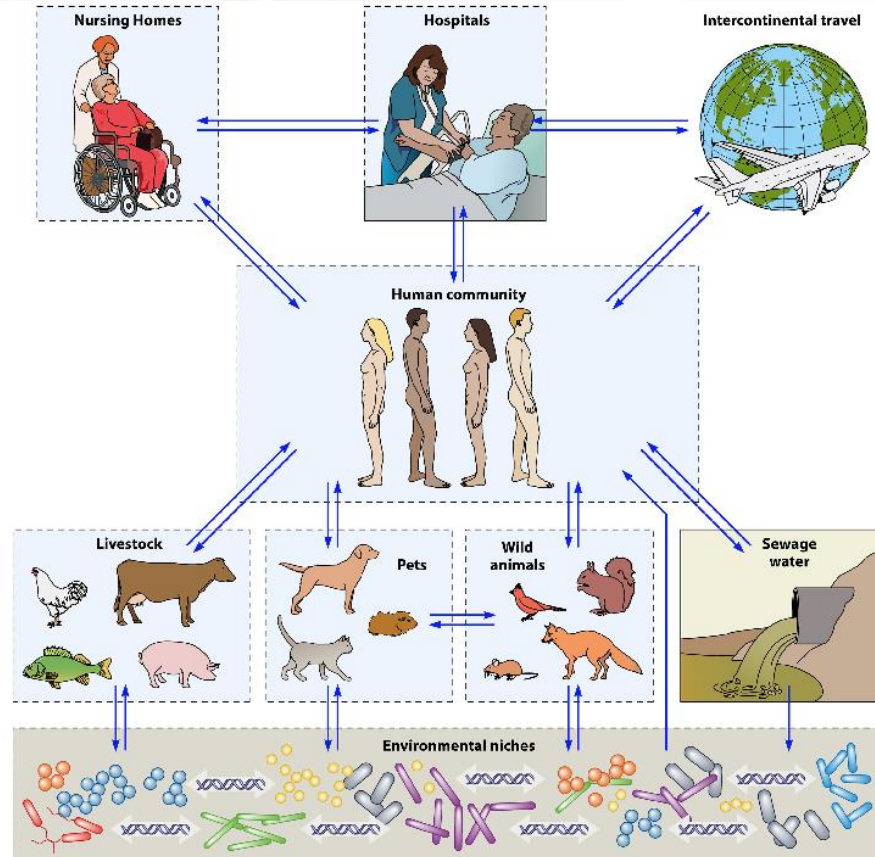


FIG 3 Representation of the main digestive or environmental reservoirs of ESBL-E to which the worldwide human community belongs and is also exposed. Each independent reservoir is included in a dashed black outline, inside which cross-transmission may occur. Arrows show the flux of ESBL-E from one reservoir to another. Environmental niches comprise mainly water, soils, and plants, where genetic material exchanges between bacteria of digestive and/or environmental origin occur.

Trends in human fecal carriage of extended-spectrum β -lactamases in the community: toward the globalization of CTX-M. Woerther PL and al. *Clin Microbiol Rev.* 2013 Oct;26(4):744-58



Votre vie,
notre combat



TWO TARGETS

» *Escherichia coli*

» *Pseudomonas aeruginosa*

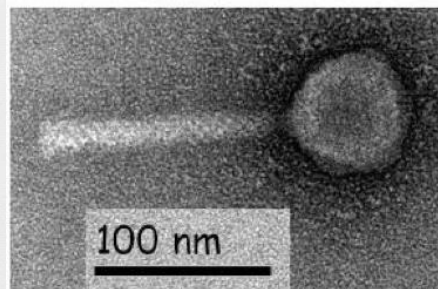
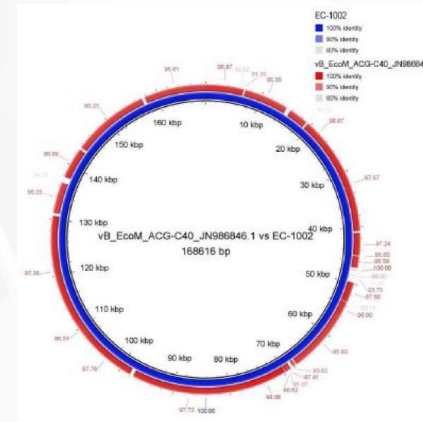
- » Antibiotic pressure is a major risk factor for rectal colonization by multidrug-resistant *Pseudomonas aeruginosa* in critically ill patients. Antimicrob Agents Chemother. 2014 Oct;58(10):5863-70.
- » An integrated approach to control a prolonged outbreak of multidrug-resistant *Pseudomonas aeruginosa* in an intensive care unit. Clin Microbiol Infect. 2014 Apr;20(4):O207-15
- » Antibiotic strategies for eradicating *Pseudomonas aeruginosa* in people with cystic fibrosis. Cochrane Database Syst Rev. 2014 Nov 10;11:



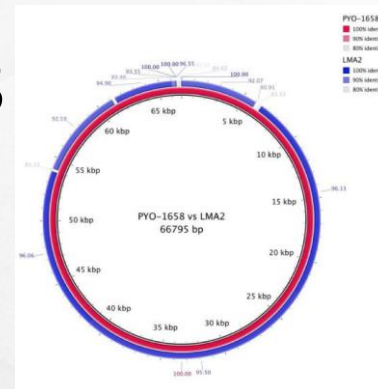
FEATURE OF PHAGES



EC-1002



PYO-1658





Votre vie,
notre combat



PP0121 AND PP1131

- **PP0121**: Mix of 13 natural lytic phages against *Escherichia coli*
- **PP1131**: Mix of 12 natural lytic phages against *Pseudomonas aeruginosa*

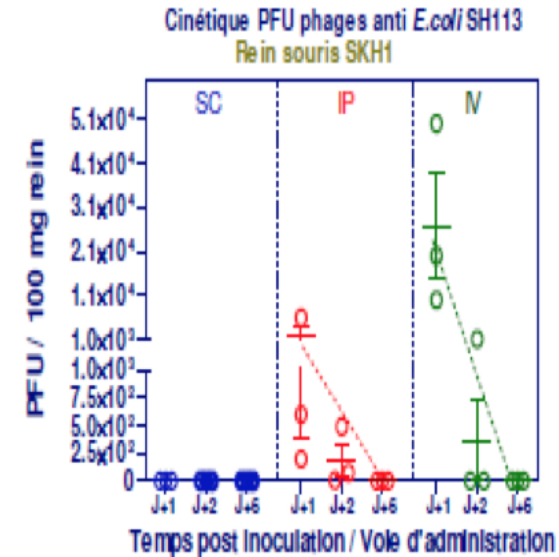
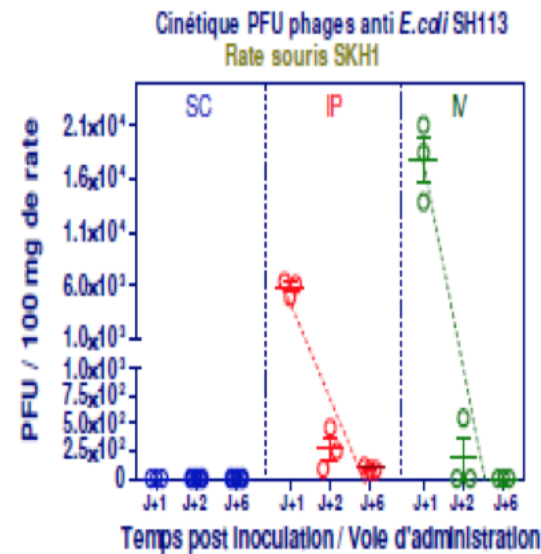
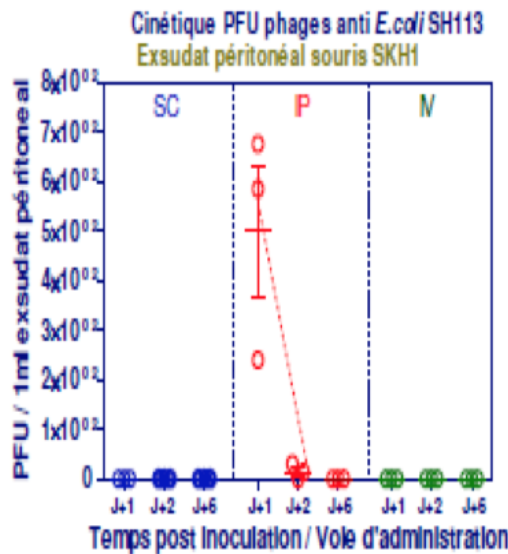


MINISTÈRE
DE LA DÉFENSE

National Institute of Allergy and Infectious Diseases
BACTERIOPHAGE THERAPY
JULY 20-21 2015

PK PP0121 (E COLI)

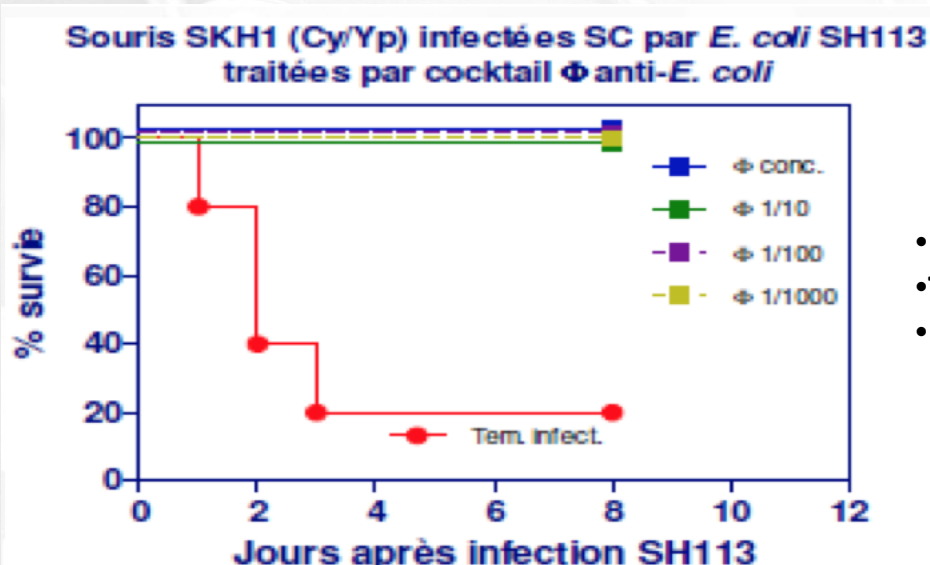
Injection of 100µl of cocktail at 10^8 PFU



With PP1131, identical results were observed

INFECTED IMMUNOSUPPRESSED MICE

Jour	-3	-2	-1	0	1	2	3	4
	1,5mg Cy	Burn	1,5mg Cy	Infection	1,5mg Cy			
Mode injection	IP	Yperite	IP	SC 10 ⁷ cfu	IP			
PHAGE				SC 6h post-infection				



CONCLUSIONS :

- No Treatment: SR= 20%
- Treated J0 (Infection +6h) by SC : SR= 100%
- Dilution of cocktail from 10⁸ to 10⁵ PFU/ml

PRE-CLINICAL SUMMARY

	Cocktail anti COLI		Cocktail anti PYO	
	mice	Mini-pigs	mice	Mini-pigs
Characterization of ϕ	✓		✓	
Efficacy SC, IP, IV	✓		✓	
Innocuousness SC, IP, IV	✓		✓	
PD via SC, IP, IV	✓		✓	
Doses	✓		✓	
Cutaneous tolerance		✓		✓
Innocuousness IV		✓		✓
PD via IV		✓		✓



Votre vie,
notre combat



BIOPRODUCTION PROCESS

1. Development of cocktails : PHERECYDES PHARMA®(RD)
2. Transfer of technology CLEAN CELLS®
3. Validation of CC as Pharmaceutical manufacturer
4. GMP environment
5. Production of Investigationnal Medicinal Products
6. Approval of clinical trial by 3 national authorities and ethical committees





Votre vie,
notre combat



COCKTAILS

- » Limit the emergence of resistant strains to phages
- » Limit the risk of failure
- » Natural lytic phages: regulatory tolerance
- » Pre-clinical tests available (efficacy and safety)
- » Bioproduction in GMP environnement
 - » **Quality-controlled small-scale production of a well-defined bacteriophage cocktail for use in human clinical trials.** Merabishvili M ad al. PLoS One. 2009;4(3)
 - » **Quality and safety requirements for sustainable phage therapy products.** Pirnay and al. Pharm Res. 2015 Jul;32(7):2173-9
- » Limited data on stability





*Votre vie,
notre combat*



II- CLINICAL STUDY



MINISTÈRE
DE LA DÉFENSE

National Institute of Allergy and Infectious Diseases
BACTERIOPHAGE THERAPY
JULY 20-21 2015



Votre vie,
notre combat



ORGANIZATION

- » International
- » Multi centric study
- » *In-hospital* patients
- » Hospitalization in intensive care units
- » Close cooperation with regulatory agencies: French / Swiss / Belgian / EMA
- » Respect of good medical practices
- » Standardization of care +++





Votre vie,
notre combat



MINISTÈRE
DE LA DÉFENSE



Coordination and PI



PHERECYDES
PHARMA

Sponsor and co-coordination



France
Europe
Innovation

CENTRE HOSPITALIER
Saint Joseph • Saint Luc

CHU
de Liège



CHU de Nantes

statitec



National Institute of Allergy and Infectious Diseases
BACTERIOPHAGE THERAPY
JULY 20-21 2015



*Votre vie,
notre combat*



MAIN OBJECTIVES

» Main objective: View from physicians

Proof of concept of efficacy

» Use of phages in treatment of human bacterial infections

» Second objective: View from regulators

» SAFETY





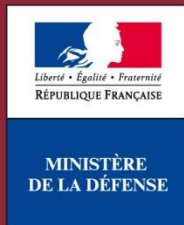
Votre vie,
notre combat



OTHER OBJECTIVES

- » Causes of failure
- » Evolution of local flora
- » Healing improvement
- » Modulation of immune response
- » Impact on gut flora
 - » **Phage therapy: the Escherichia coli experience.** Brüssow H. Microbiology. 2005 Jul;151(Pt 7):2133-40
 - » **Oral T4-like phage cocktail application to healthy adult volunteers from Bangladesh.** Sarker SA and al. Virology. 2012 Dec 20;434(2):222-32
- » Bio distribution: absorption, clearance, elimination...
- » Interaction with antibiotics
- » MDR bacteria...

In only 36 months





*Votre vie,
notre combat*



PRIMARY OUTCOME

Time for reduction of bacterial load by decrease of two modes (2 logs reduction) relative to D0 on plate culture



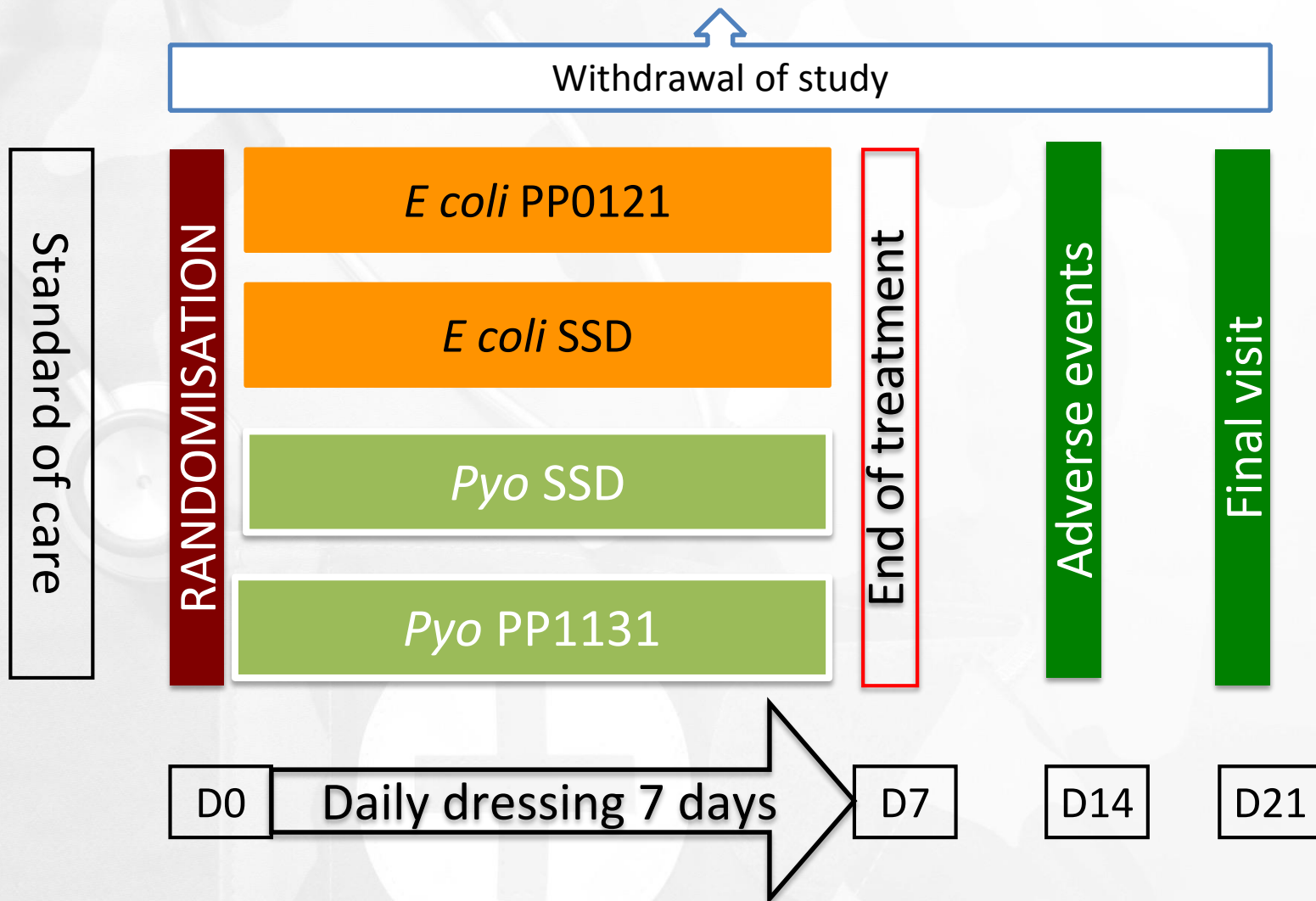
GLOBAL DESIGN



Votre vie,
notre combat



MINISTÈRE
DE LA DÉFENSE



STANDARD OF CARE

Clinical suspicion of infection

Bacteriologic sample : Swab

Probabilistic treatment: Povidone
iodine (Silver free dressing)

Biological confirmation of
bacterial species



Votre vie,
notre combat



INCLUSION CRITERIONS

- » Man or woman
- » Adult
- » Informed consent obtained
- » In-hospital patient in a burn unit
- » Infected wound: SFETB standards
- » *E coli* or *Pseudomonas aeruginosa*, whatever antimicrobial resistance





Votre vie,
notre combat



EXCLUSION CRITERIONS

- » Pregnant or breastfeeding woman
- » Intercurrent condition requiring a treatment which may interfere with analysis results: such as high dose of chronic corticotherapy, immunosuppressive medication, oncologic chemotherapy
- » Patient included in an interventional research protocol with therapeutic intervention still ongoing upon inclusion time or having participated into anti-infective drug trials during the previous month. Patient previously included in the study
- » Vulnerable population
- » Polymicrobial infections : Staph + coli / coli + pyo
- » Patient for whom treatment limitation or withdrawal during study period is considered
- » *General or local Known sensibilization to sulfamides*



MINISTÈRE
DE LA DÉFENSE



*Votre vie,
notre combat*



RANDOMIZATION

- » Stratification on antibiotics
- » Impossible to avoid antibiotic use
- » Antibiotics are free of use
- » Consistent to current recommendations

Guidelines for use of antibiotics in burn patient at the acute phase. Ravat F and al. Ann Fr Anesth Reanim. 2009 Mar;28(3):265-74



CONTROL GROUP

- » 1% Silver sulfadiazine cream
- » Broad spectrum antiseptic activity: *S aureus*, *E coli*, *Pyo*, *Klebsiella sp*, *Proteus*, *Candida*
- » Instead of :
 - Mafenide acetate (Sulfamylon®): Temporary use
 - Colimycin preparation : Local preparation
 - Hypochlorite Bath
- » Experts agreement
- » Several Known adverse effects



*Votre vie,
notre combat*



MINISTÈRE
DE LA DÉFENSE

National Institute of Allergy and Infectious Diseases
BACTERIOPHAGE THERAPY
JULY 20-21 2015



*Votre vie,
notre combat*



III- SITUATION



MINISTÈRE
DE LA DÉFENSE

National Institute of Allergy and Infectious Diseases
BACTERIOPHAGE THERAPY
JULY 20-21 2015

ADJUSTMENTS

» Increase duration of study

36 months

» Increase number of investigation sites

11 centers

NNT = 220 patients / 11 months

» Adjustment in cocktail:

- Quantity / Quality of phages
- Presentation of clinical batches



Votre vie,
notre combat



REGULATORY DISCUSSIONS

- » Management of adverse effects:
 - » control group: Silver Sulfadiazine
 - » « *A priori* » Risk assessment
- » Interactions with ongoing antibiotics
 - » With or without effect on the treated strain
- » Education and information of teams



MINISTÈRE
DE LA DÉFENSE



*Votre vie,
notre combat*



NEXT DEVELOPMENTS

- » DSMB every 3 months, 50 patients
- » Open data to agencies
- » Specific management of adverse effects
- » Non blind for physicians
- » Results will be known in 1 year
- » Authorizations from 3 medicines agencies





*Votre vie,
notre combat*



WHAT HAVE WE LEARNT ?

- » Too many questions to answer in a single study: efficacy, safety, metabolism...
- » In vivo/vitro, Animal/human differences
- » Collaborative work with many different components





*Votre vie,
notre combat*



CONCLUSION

- » PHAGOBURN is developed in an Evidence Based Medicine framework
- » Efficacy and monitoring of AE of 2 different drugs : PP0121/ PP1131
- » Each drug is composed with a dozen of alive active substances...
- » Extrapolation to a « class of drug »
- » Whatever the results, more evidence will be necessary

